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NÖTIFICATION CONCERNING SÜBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SAEKI, Norio 9th floor, Taka-ai Building 15-2, Nihonbashi 3-chome Chuo-ku, Tokyo 103-0027 Japan

JA50470

| Date of mailing (day/month/year) 15 August 2003 (15.08.03) | |
|--|--|
| Applicant's or agent's file reference JA504705 | IMPORTANT NOTIFICATION |
| International application No. | International filing date (day/month/year) |
| PCT/JP03/07333 | 10 June 2003 (10.06.03) |
| International publication date (day/month/year) | Priority date (day/month/year) |
| Not yet published | 10 June 2002 (10.06.02) |

THE UNIVERSITY OF EDINBURGH et al

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the
 International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise
 indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority
 document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority datePriority application No.Country or regional Office or PCT receiving OfficeDate of receipt of priority document10 June 2002 (10.06.02)0213286.8GB27 June 2003 (27.06.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

Patricia Blanchet (Fax 338 9090)

Telephone No. (41-22) 338 9655

PCT

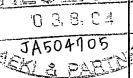
NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SAEKI, Norio
9th floor, Taka-ai Building
15-2, Nihonbashi 3-chome
Chuo-ku, Tokyo 103-0027
Japan



| PORTANT NOTIFICATION |
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| |
| date (day/month/year) 03 (10.06.03) |
| month/year) 002 (10.06.02) |
| • |

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Priority date Priority application No.

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Date of receipt of priority document

10 June 2002 (10.06.02)

0213286.8

GB

NR

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

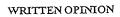
Patricia Blanchet (Fax 338 9090)

Facsimile No. (41-22) 338.90.90

Telephone No. (41-22) 338 9655

PATENT COOPERATION TREATY

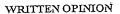
| From the INTERNATIONAL PRELIMINARY EXAMINING AUTHO | DRITY | • | |
|---|---|--|---|
| То: | | PCT | 04:2.2 |
| SAEKI NORIO | | WRITTENOPINION | JA 50 4 7 0 5 |
| 9th floor, Taka-ai Building 15-2, Nihonbashi 3-chome | | (PCT Rule 66) | - Labor |
| chuo-ku, Tokyo 103-0027 JAPAN | Date of mailing (day/month/year) | 24. 2. 2004 | |
| Applicant's or agent's file reference JA504705 | REPLY DUE | within 2 months the above date of mailing | from |
| PCT/JP 03/7333 10. | date (day/month/year) | Priority date (day/month/yea | · . |
| International Patent Classification (IPC) or both national class Int.Cl 7 C07K7/06, A61K38/08, A61K38/55, 2 | • | 14,A61P27/02,A61P43 | 3/00 |
| Applicant THE UNIVER | SITY OF EDI | NBURGH | |
| 1. This written opinion is the | to novelty, inventive step with regard to novelty, in a statement tion pplication cant may, before the expir where appropriate, by an tents, see Rules 66.8 and adments, see Rule 66.4. endments and/or argumen niner, see Rule 66.6. ination report will be esta | nventive step or industrial apportunity of that time limit, request mendments, according to Rule 66.9. | licability; t this Authority to 66.3. |
| Name and mailing address of the IPEA/JP | Authorized officer | T . | 47 0525 |
| Japan Patent Office | | MUKASA | 4B 9735 |
| 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japa | 81-3-3581-1101 Ext. 34 | 48 | |



International application No.

PCT/JP 03/7333

| 7777-1 | | | |
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International application No. PCT/JP 03/7333

| /. | Reasoned statement under Rule citations and explanations supp | 66.2(a)(ii) worting such s | rith regard to novelty, inventive step or industrial applicabili statement | -y; |
|--------|---|----------------------------|---|---------|
| ١. | Statement | | | |
| | Novelty (N) | Claims Claims | 1-7 | YES |
| | Inventive step (IS) | Claims Claims | 1-7 | YES |
| | Industrial applicability (IA) | Claims Claims | 1-7 | YES |

2. Citations and explanations

D1: WO 01/62291 A1(FUSO PHARM IND LTD) 2001.08.30

D2:WO 01/47556 A1(FUSO PHARM IND LTD)2001.07.05

D3:D'Alessio S et al, Inhibition of adamalysin II and MMPs by phosphonate analogues of snake venom peptides., Bioorg Med hem.,1999,Vol.7,No.2,p.389-94., especially page 390 Scheme 1

D4:WO 97/25351 A2(MILLENNIUM PHARM INC)1997.07.17 ,especially page 5 \sim 7

The subject matters of claim 1 through 7 does not involve an inventive step over D1,D2, D3 and D4 for the following reasons.

D1 describes a peptide(SLIGRL-NH2) activating PAR-2 which are useful in controlling gastric hydrochloric acid secretion, promoting digestive mucous secretion, protecting gastric mucosae, repairing gastric tissues and preventing and treating gastric diseases.

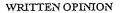
D2 describes a peptide(SLIGRL-NH2) activating PAR-2 which can be used in the treatment of promoting lacrimal secretion.

D3 describes a peptide inhibitor of metaloproteinase which is modified by 2-furancarboxylic acid in the N-termini(D3 p.390 Scheme 1).

D4 describes a peptide which mimic the conserves amino acid motif LDTSL of MAdCA M-1 and which have groups (for example, aryl group)bonded to the N-and C-termini(D $4 p.5 \sim 7$).

D3 and D4 disclose modifying the N-termini of peptide , and the skilled person in the art would easily conceive the idea of modifing the peptide in D1 and D2 .

It would be obvious to the person skilled in the art to truncate the peptide in N-termini, and no unexpected effects are indicated except compounds which contains 2-furancarboxylic acid, Example 6,16,17, and 18.



International application No. PCT/JP 03/7333

Supplémental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Claim 1-7 is not supported by the description as required by Article 6 PCT. The reason therefor is the following: aryl group in claim 1 contains a lot of structure, but in the description, only a few structures are disclosed.

We searched the subject matter of claim 1-7 which is supported by the description, Z -(CH2)n represents in the example 1-18,AA1-AA2 represents Lys-Val or Arg-Leu, and R represents -OH or -NH2.

ATTENTION

Forms and Preparation Points for Documents to be Submitted

Forms for a written reply and a written amendment shall be prepared in conformity to Article 62 (Form 23) and Article 31 (Form 15) of Enforcement Regulations of Law Concerning the International Application of the Patent Cooperation Treaty and Related Matters.

- The paper sheet used is set to Row A, No. 4 (horizontal writing 21cm, 29.7cm) of the Japanese Industrial Standards; only one side of a flexible, strong, smooth, lusterless, and durable paper sheet with no fold is used
- with its shorter side at the top; and unnecessary characters, signs, frame lines, ruled lines, etc. shall not be written on this paper.
- 2. The paper shall be free of creases and tears.
- 3. Margins shall be set to at least 2cm at the upper edge, the right edge, and the bottom edge of the paper sheet, and 2.5cm at the left edge. In principle, the margins shall not exceed 4cm at the upper edge and the left edge, or 3cm at the right edge and the bottom edge. In theses cases, the margins are left completely blank. The document number (provided it is described in the request) may be added in the margin corner of the upper edge and within 1.5cm of the upper edge.
- 4. The written reply shall be a typed or printed manuscript so that an arbitrary number of copies may be directly made by photograph, electrostatic method, photographic offset, or microfilm.
- 5. In all the paper sheets of the written reply, serial numbers starting from 1 in Arabic numerals shall be added in the center of the top or bottom edge of the paper sheet (except for the margin parts).
- 6. In cases of a typed manuscript, the space between the lines shall be set to at least 5mm. In case of using Roman letters in Remarks 11 and 14, the width shall be set to 1.5 letters.
- 7. Items mentioned shall be written in characters of No. 4 type (Roman letters used for Remarks 11 and 14 are set to not less than 0.21cm in height in capital letters), wherein the color used shall be dark and non-fading, and the characters shall fulfill the requirements prescribed in Remark 4.
- 8. In the column "Indication of International Application," where an applicant has already received the notification of the international application number from the Patent Office, the number shall be described in such a manner as "PCT/IPO/OOOO," where the applicant has not yet received the notification of the international application number, the date of submitting the international application shall be described in the order of date, month and year in such a manner as "international application submitted on OOOOO" (as for the year, only the last two figures of the Christian Era shall be described), and the document number (provided it is described in the request) shall be also described therein.
- 9. The "Name of Applicant" shall be described as the full name in the order of family name and first name in the case of an individual person; in the case of a juridicial body, the name shall be described.
- 10. The "Address" shall be described in detail such as "Japan, prefecture, county, village, major article, minor article, plot number, and house number" and the postal code shall be also stated.
- 11. The transliteration of the name and the address of the applicant or their
- translation into English shall be also added thereto using Roman letters.

 12. In the column "Nationality," the name of the country of the applicant or
- the representative shall be described.

 13. In the column "Address," the name of the country in which the applicant or the representative resides shall be described.
- 14. In the case of describing the name of a country, the name of the country designated by the Commissioner shall be written in Japanese and English.
- 15. In the column "Representative," the name of the representative shall be described and the applicable one from among "lawyer," "patent attorney," and "legal representative" shall be described before the name of the representative.
- 16. Where a representative is stated, the seal of the applicant is not necessary; if there is no representative, the column "Representative" need not be provided.
- In each paper sheet, erasure, correction, overwriting, and inserted lines are not permitted in principle.
- 18. The paper sheets for the written reply shall be filed with, for example, a clip so as to be easily separated or re-filed.
- In the "Address," only one address of each applicant, representative, attorney, or sub-attorney shall be described.
- 20. In the column "Sub-Attorney," the name of the sub-attorney shall be described and the applicable name from among "lawyer" or "patent attorney" shall be described before the name of the sub-attorney.
- 21. Where a sub-attorney is stated, the seal of an attorney is not necessary; if

there is no sub-attorney, the column "Sub-attorney" need not be provided.

22. The Christian Era or Gregorian Calendar shall be used for the date. Figures of the day, figures of the month, and last two figures of the year shall be expressed in Arabic numerals respectively in this order, and a period shall be added after the figures of the day and the month (for example, March 30th, 1978 shall be written as "30.03.78"). When using another era or calendar, the Christian Era or Gregorian Calendar shall be added thereto.

Form 23 (Related to Article 62) REPLY(ARGUMENT)

To: Examiner of the Patent Office

- 1. Identification of the International Application
- 2. Applicant (Common Representative)
 Name: seal

Address:

Country of Nationality: Country of residence:

Agent Name:

seal

Address

- 4. Date of Notification
- 5. Subject Matter of Reply(Argument)
 - List of Attached Documents

[Remarks]

- In case an amendment is made pursuant to the order in the provisions of Article 6 of the Patent Law, the title shall be set to "AMENDMENT (amendment based upon the order in the provisions of Article 6 of said Law)"; in case an amendment is made pursuant to the provisions of Article 11 of said Law, the title shall be set to "AMENDMENT (amendment based upon the provisions of Article 11 of said Law)"; in case an amendment is made pursuant to the order in the provisions of Item 2 of Article 1 of the Patent Law Enforcement Order, the title shall be set to "AMENDMENT (amendment based upon the order in the provisions of Item 2 of Article 1 of said Order)"; in case an amendment is made pursuant to the provisions of Item 1 of Article 27-3, the title shall be set to "AMENDMENT (amendment based upon the provisions of Item 1 of Article 27-3)"; in case an amendment is made pursuant to the order in the provisions of Item 1 of Article 28, the title shall be set to "AMENDMENT (amendment based upon the order in the provisions of Item 1 of Article 28)"; in case a flexible disk is submitted pursuant to the provisions of Item 3 of Article 50-3, the title shall be set to "SUBMISSION OF FLEXIBLE DISK Based Upon the Provisions of Item 3 of Article 50-3"; in case a flexible disk is submitted pursuant to the order in the provisions of Item 5 of Article 50-3, the title shall be set to "SUBMISSION OF FLEXIBLE DISK Based upon the Order in the Provisions of Item 3 of Article 50-3"; in case a document describing the sequence listing is submitted pursuant to the order in the provisions of Item 5 of Article 50-3, the title shall be set to "SUBMISSION OF DOCUMENT DESCRIBING SEQUENCE LISTING Based upon the Order in the Provisions of Item 5 of Article 50-3"; and in case an amendment is made pursuant to the order in the provisions of Item 8 of Article 50-3, the title shall be set to "AMENDMENT (amendment based upon the order in the provisions of Item 8 of Article 50-3")
- 2. If an examiner of the Patent Office has given an opportunity for submitting a written reply or its amendment, the reply or the amendment shall be submitted to said examiner of the Patent Office, and it shall be submitted to the Commissioner of the Patent Office for any other cases.
- In the column "Object of Amendment," the name of the document to be amended and the passage to be amended shall be described in such a manner as "Request II, Column of Applicant."
- In the column "Contents of Amendment," "as per an accompanying sheet" shall be described and the matters to be amended shall be pointed out, and a replacement paper sheet for the amendment shall be appended. However, where the whole of the paper sheet is deleted as a result of the amendment, where the amendment is made pursuant to the order in the provisions of Article 6 of the Patent Law, Item 2 of Article 1 of the Patent Law Enforcement Order, Item 1 of Article 28 or Item 8 of Article 50-33, or where the amendment is made pursuant to the provisions of Item 1 of Article 27-3, there is no need to use a replacement paper sheet if the matters related to the amendment can be easily re-written in the original text. Where a replacement paper sheet for an amendment provided for in Article 11 of the Patent Law is appended, and the matter related to the amendment is a deletion or an addition of only a part of a passage or a minor correction, the amendment may be made in the copy of the written amendment that has been submitted before instead of using a replacement paper sheet provided it does not affect the neatness and direct copying of
- the paper sheet.

 5. When the scope of claims is amended, a replacement paper sheet

describing the scope of claims related to said amendment as follows shall be appended.

- a) When a new item is added to the scope of claims, the number given to the last item of the scope of claims before being amended shall be described before the item to be added in such a manner as "O (added)."
- b) When any item of the scope of claims is deleted, the number given to the item of the scope of claims to be deleted shall be described in such a manner as "O (deleted)."
- When the scope of claims is amended without increasing or decreasing the number of items of the scope of claims, the same number as that for the item of the scope of claims before being amended shall be given to the amended item of the scope of claims in such a manner as "O after being amended."
- 5. When a flexible disk is submitted pursuant to the provisions of Item 3 of Article 30-3 or when a flexible disk is submitted pursuant to the order in the provisions of Item 5 of Article 60-3, descriptions shall be made as follows.
 - In the column "7. List of Attached Documents," the following items shall be described.
 - 5. List of Attached Documents
 - (1) Flexible disk that records code data concerning sequence listing: 1 piece
 - (2) Statement: 1 copy
 - Ocument describing information about the recording method, etc. of a flexible disk: 1 copy
 - b) In principle, the "Statement" shall be prepared pursuant to the sample shown below. The item "Indication of International Application" shall be described pursuant to Remark 15 described hereunder.

(Sample)

STATEMENT

To: the Commissioner of the Patent-Office

I hereby declare that the base sequence and amino acid sequence recorded in the flexible disk attached to this document have faithfully encoded the base sequence and amino acid sequence described in the specification without making any change of the contents.

Day month, year

Indication of International Application

Title of the Invention

Applicant or Agent

- c) "Document describing information about the recording method, etc. of a flexible disk" shall be made, in principle, by providing and describing such items as "Name of Applicant," "Name of Agent," "Indication of International Application," "Title of the Invention," "Character Code Used," "Name of a File Recording the Sequence," and "Person to be Contacted (phone number and name of the person in charge)."
- Columns "5. Object of Amendment" and "6. Contents of Amendment" shall not be provided.
- When a document describing the sequence listing pursuant to the order in the provisions of Item 5 of Article 60-3, the following item shall be described in the column "7. List of Attached Documents," and columns "5. Object of Amendment" and "6. Contents of Amendment" shall not be provided.
- 5. List of Attached Documents
- (1) Document describing the sequence listing: 1 copy
- 8. The paper sheet used is set to Row A, No. 4 (horizontal writing 21cm, 29.7cm) of the Japanese Industrial Standards; only one side of a flexible, strong, smooth, lusterless, and durable paper sheet with no fold is used with its shorter side at the top; and unnecessary characters, signs, frame lines, ruled lines, etc. shall not be written on this paper.

The paper shall be free of creases and tears.

- 10. Margins shall be set to at least 2cm at the upper edge, the right edge, and the bottom edge of the paper sheet, and 2.5cm at the left edge. In principle, the margins shall not exceed 4cm at the upper edge and the left edge, or 3cm at the right edge and the bottom edge. In theses cases, the margins are left completely blank. The document number (provided it is described in the request) may be added in the margin corner of the upper edge and within 1.5cm of the upper edge.
- 11. The written amendment shall be a typed or printed manuscript so that an arbitrary number of copies may be directly made by photograph, electrostatic method, photographic offset, or microfilm.
- 12. In all the paper sheets of the written amendment, serial numbers starting from 1 in Arabic numerals shall be added in the center of the top or bottom edge of the paper sheet (except for the margin parts).
- 13. In cases of a typed manuscript, the space between the lines shall be set to

- at least 5mm. In case of using Roman letters in Remarks 11 and 14, the width shall be set to 1.5 letters.
- 14. Items mentioned shall be written in characters of No. 4 type (Roman letters used for Remarks 11 and 14 are set to not less than 0.21cm in height in capital letters), wherein the color used shall be dark and non-fading, and the characters shall fulfill the requirements prescribed in Remark 9.
- 15. In the column "Indication of International Application," where an applicant has already received the notification of the international application number from the Patent Office, the number shall be described in such a manner as "PCT/JPOO/OOOO," where the applicant has not yet received the notification of the international application number, the date of submitting the international application shall be described in the order of date, month and year in such a manner as "international application submitted on OOOOO" (as for the year, only the last two figures of the Christian Era shall be described), and the document number (provided it is described in the request) shall be also described therein.
- 16. The "Name of Applicant" shall be described as the full name in the order of family name and first name in the case of an individual person; in the case of a juridicial body, the name shall be described.
- 17. The "Address" shall be described in detail such as "Japan, prefecture, county, village, major article, minor article, plot number, and house number" and the postal code shall be also stated.
- 18. The transliteration of the name and the address of the applicant or their translation into English shall be also added thereto using Roman letters.
- In the column "Nationality," the name of the country of the applicant or the representative shall be described.
- In the column "Address," the name of the country of the applicant or the representative shall be described.
- 21. In the case of describing the name of a country, the name of the country designated by the Commissioner shall be written in Japanese and English.
- 22. In the column "Representative," the name of the representative shall be described and the applicable one from among "lawyer," "patent attorney," and "legal representative" shall be described before the name of the representative.
- 23. Where a representative is stated, the seal of the applicant is not necessary; if there is no representative, the column "Representative" need not be provided.
- 24. In each paper sheet, erasure, correction, overwriting, and inserted lines are not permitted in principle.
- 25. The paper sheets for the written reply shall be filed with, for example, a
- clip so as to be easily separated or re-filed.

 26. In the "Address," only one address of each applicant, representative,
- attorney, or sub-attorney shall be described.

 27. In the column "Sub-Attorney," the name of the sub-attorney shall be described and the applicable name from among "lawyer" or "patent attorney" shall be described before the name of the sub-attorney.
- 28. Where a sub-attorney is stated, the seal of an attorney is not necessary; if there is no sub-attorney, the column "Sub-attorney" need not be provided.
- 29. The Christian Era or Gregorian Calendar shall be used for the date. Figures of the day, figures of the month, and last two figures of the year shall be expressed in Arabic numerals respectively in this order, and a period shall be added after the figures of the day and the month (for example, March 30th, 1978 shall be written as "30.03.78"). When using another era or calendar, the Christian Era or Gregorian Calendar shall be added thereto.

 | Example Related to Article 31)

| rutin 1) (Kelated to Altiele): | •) |
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| CORRECTION(AMENDMEN | T) . |
| To: Commissioner of the Pate | nt Office |
| (To: Examiner of the Patent | |
| 1. Identification of Internation | al Application |
| 2. Applicant (Common Repres | sentative) |
| Name: | Signature(Seal) |
| Address: | |
| Country of nationality: | • |
| Country of residence: | • |
| 3. Agent | |
| Name: | Signature(Seal) |
| Address: | • |
| 4. Date of Invitation | |
| 5. Item to be Corrected(Amen | ded) |
| 6. Subject Matter of Correction | n(Amendment) |
| 7. List of Attached Documents | |
| | |